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C–H Arylation

Towards New Tricyclic Motifs: Intramolecular C–H Arylation as the Key Step in a Formal [3+3] Cyclocondensation Strategy

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Abstract: Tricyclic scaffolds structurally related to the well-known benzodiazepine class of drugs show diverse biological activities strikingly different from those of their benzodiazepine counterparts. Interested by this scaffold-hopping perspective, we previously developed a continuous-flow method for the conversion of benzodiazepinediones into oxazoloquinolinones. Attempted extension of this synthetic route to the corresponding oxazolonaphthyridinone scaffolds met with limited success, however. This encouraged us to develop a different approach to pyridine-based tricyclic motifs. In line with our interest in scaffold hopping, in this paper we describe a general, convergent [3+3] cyclocondensation approach to [1,3]oxazolo[4,5-*c*]-1-naphthyridin-4(5*H*)-ones. The key synthetic steps in this approach are: (1) the construction of an amide linkage connecting two peripheral heterocycles; and (2) a palladium-catalysed intramolecular C–H arylation to complete the tricyclic scaffold.

Introduction

Drugs of the benzodiazepine class have been among the most highly prescribed medication globally since their discovery in the 1950s, and the search for structurally related biologically active compounds is of major relevance to the pharmaceutical industry.[1] Previous work in our group dealing with the construction of benzodiazepinediones (BZDs) **2** (Figure 1) led unexpectedly to the isolation of tricyclic compounds, which were later identified as oxazoloquinolinones (OQOs) **1**.[2,3] Not only was the new cascade reaction that converts BZDs **2** into OQOs **1** of interest, but also compounds **1** themselves. These compounds have numerous biological activities, including Gly/NMDA-receptor antagonism (NMDA = *N*-methyl-D-aspartate),[4] modulation of GABA-receptor inverse agonism (GABA = γ-aminobutyric acid),[5] and inhibition of multidrug-resistance-associated protein 1 (MRP1).[6] Intrigued by this ability to entirely switch biological activities, we established a continuous-flow method for the conversion of BZDs **2** into OQOs **1** in yields of up to 98 %.[3] Having established this optimised transannular rearrangement of an activated lactam[7] encompassing cascade (TRALEC) reaction, extension of the approach to the preparation of the largely unexplored oxazolonaphthyridinones (ONOs) **4** seemed an appealing prospect. Unfortunately, preliminary research in our group quickly led us to observe that the problematic preparation of pyridodiazepinedione (PZD) **11** as the TRALEC reaction precursor was undermining the feasibility of this synthetic route (Scheme 1). In our preliminary investigation, aza-anthranilic derivative **8** was converted into ester compound **9**, and this was subsequently saponified and cyclised to give PZD **11** in 9 % overall yield. Using a microwave-assisted TRALEC reaction to convert PZD **11** into ONO **12**, the overall yield of the synthetic sequence was just 3 %. Fiakpui and Knaus already noted correctly in 1987 that very few pyridodiazepines have

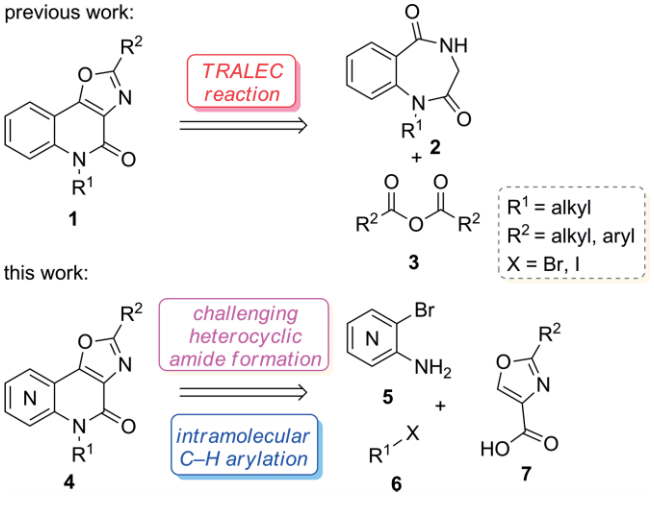
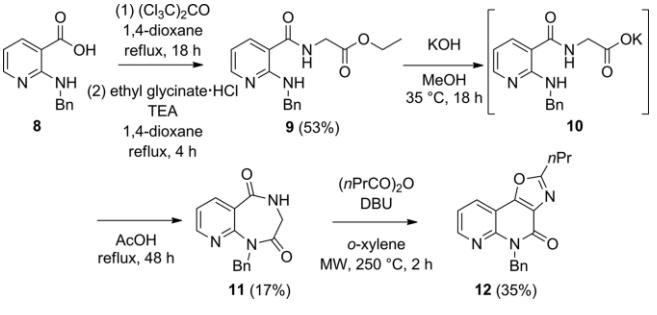


Figure 1. Routes to biologically active tricyclic motifs.



Scheme 1. Synthesis of PZD **11** and verification of its TRALEC reaction. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

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been studied clinically, as their syntheses usually require aminopyridinecarboxylic acid precursors, and give low overall yields.[8] Based on a recent database search, we can conclude that this statement about the synthetically challenging pyridodiazepines is still remarkably up to date.

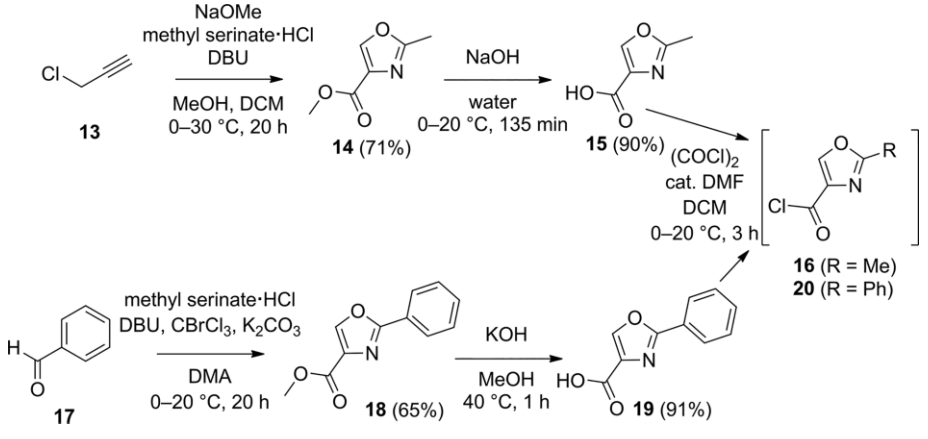
It is clear that a different synthetic strategy is required for obtaining the desired scaffolds **4**, avoiding the need for the TRALEC reaction and the preparation of its diazepinedione precursors. An interesting alternative approach to similar tricyclic motifs was developed by Hodgetts and Kershaw, who constructed the OQO motif **1** by assembling the key heterocycle in a [3+3] cyclocondensation fashion.[9] Formation of the amide bond in this strategy is straightforward, and the aryl–aryl (Ar–Ar) bond was formed by a Suzuki coupling, allowing the full [3+3] cyclocondensation to be carried out as a remarkable one-pot procedure. Although this one-pot procedure is elegant, it was deemed to be less suitable for our investigation as it would require the use of some troublesome heterocyclic boronate building blocks (unstable, low-yielding synthesis, difficult purification). Hodgetts and Kershaw also briefly evaluated intramolecular C–H arylation as another method for constructing the Ar–Ar bond, and this quickly emerged as our method of choice. Intramolecular C–H arylation using palladium in catalytic amounts was pioneered by Ames and Opalko in 1984 for the construction of diverse tricyclic motifs bearing peripheral six-membered rings.[10] It was later recognised by others that milder conditions could be used when carrying out intramolecular C–H arylation reactions on electron-rich five-membered heterocycles, and therefore an electrophilic reaction mechanism was proposed by Kuroda and Suzuki.[11] More recently, Beccalli and co-workers used palladium-catalysed C–H activation on electron-rich heterocycles for the synthesis of tricyclic motifs and for the construction of medium- and large-ring-fused heterocycles.[12,13] Not surprisingly, due to its utility in the construction of complex polycyclic molecular architectures, intramolecular C–H arylation has been extensively discussed in literature reviews of transition-metal-catalysed C–H functionalisation methods.[14–16]

In this paper, we describe a general [3+3] cyclocondensation strategy giving access to the four isomeric [1,3]oxazolo[4,5-*c*]-1-naphthyridin-4(5*H*)-one scaffolds **4**. The key synthetic steps in this strategy are (1) the construction of a challenging amide linker connecting the two peripheral heterocycles, and (2) a palladium-catalysed intramolecular C–H arylation to form the key heterocycle. To the best of our knowledge, three out of these four possible isomeric ONO scaffolds **4** have never been reported before. Also, the C–H arylation of electron-rich azoles has not been systematically investigated using all the regioisomers of a halopyridine as cross-coupling partners.

Results and Discussion

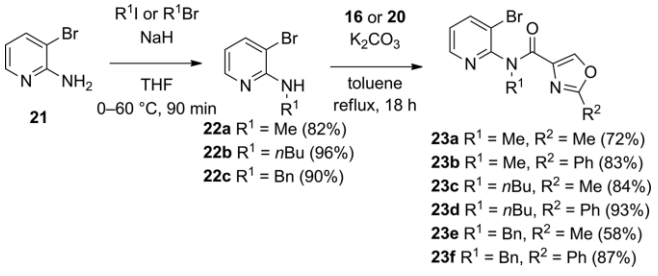
We started our investigation with the synthesis of oxazole building blocks **15** and **19** (Scheme 2). 2-Methyl-substituted oxazole ester **14** was prepared by a convenient one-pot procedure based on the work of Benoit and co-workers.[17] Oxazole ester **18**, bearing a 2-phenyl substituent, was obtained using the elegant one-pot procedure described by Graham.[18] Extension of the latter method allows the incorporation of a wide variety of aromatic and conjugated aldehydes into 2,4-disubstituted oxazoles that are otherwise not readily accessible or require a multistep synthesis. Subsequently, oxazole esters **14** and **18** were saponified to give the desired building blocks **15** and **19** in excellent yields. Finally, oxalyl chloride was the reagent of choice for the conversion, under mild conditions, of the acid-labile oxazole building blocks into their corresponding acyl chlorides **16** and **20**, which were used immediately for amide coupling reactions. Previously, we developed a base-mediated protocol to prepare challenging amides from non-nucleophilic amines and esters under flow conditions.[19] Unfortunately, in this investigation, the latter protocol could not be used to couple esters **14** and **18** with amines due to dominant side reactions resulting from the acidic nature of the 5-oxazole proton.[20]

With the oxazole building blocks and derived acyl chlorides **16** and **20** in hand, we turned our attention to the synthesis of tertiary pyridinamide cyclisation precursors **23a**–**f**, **26a**,**b**, **29a**,**b**, **32a**,**b** (Schemes 3 and 4). We envisaged that tertiary pyridinamides could be used as cyclisation precursors, as (1) an additional amide substituent implies an additional point of diversity for our intended final products, and (2) tertiary amides are

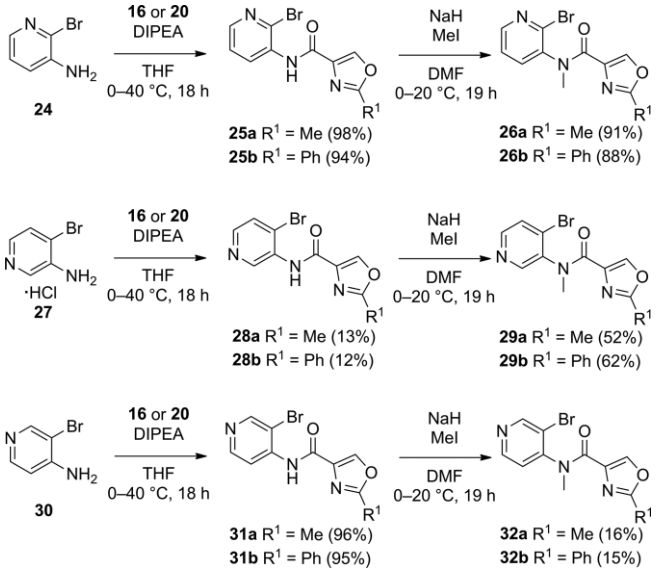


Scheme 2. Synthesis of oxazole building blocks.

known to have a lower energy barrier for amide *cis*/*trans* isomerisation, and this would favour the final intramolecular C–H arylation step. Additionally, Beccalli and co-workers claimed that tertiarisation of the amide moiety is necessary to avoid N–Pd complexation in the C–H arylation step.[12,13]



Scheme 3. Synthesis of 2-pyridinamide cyclisation precursors.



Scheme 4. Synthesis of 3- and 4-pyridinamide cyclisation precursors. DIPEA = diisopropylethylamine.

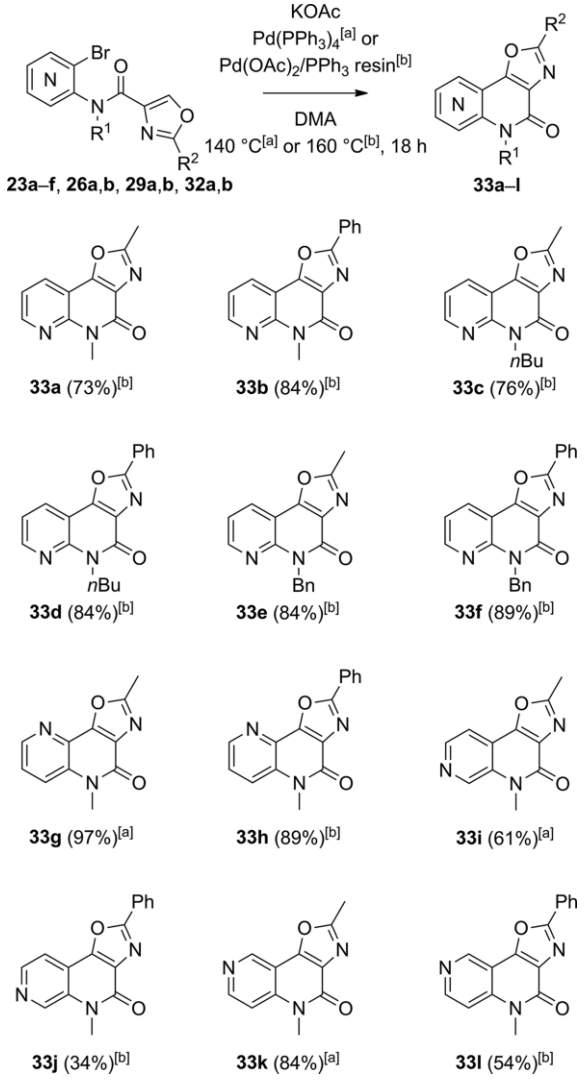
First, we investigated the preparation of 2-pyridinamide cyclisation precursors **23a**–**f**, derived from starting material 2-amino-3-bromopyridine (**21**; Scheme 3). Grig-Alexa and co-workers demonstrated that various 2-(alkylamino)-3-bromopyridines can be obtained by a simple deprotonation/alkylation reaction of **21** in anhydrous tetrahydrofuran (THF). In this way, the need for a reductive amination or acylation/reduction approach is avoided.[21] In our hands, 2-(alkylamino)-3-bromopyridines **22a**–**c** were obtained in very good to excellent yields upon deprotonation/alkylation of starting material **21**. The interesting selectivity of the reaction can undoubtedly be attributed to both the use of a near-stoichiometric amount of reagents, and an increased steric hindrance on the amino group upon monoalkylation. Bearing in mind the significant steric hindrance around the amino group in **22a**–**c**, as well as the low intrisic nucleophilicity of aminopyridines, we were initially concerned about the feasibility of coupling reactions between these compounds and acyl chlorides **16** and **20**. Although typical coupling conditions did not result in product formation, we were pleased to find that the forcing coupling conditions described by Ayitou and Sivaguru yielded the target amides **23a**–**f** in fair to excellent yields.[22]

Secondly, we investigated the preparation of 3- and 4-pyridinamide cyclisation precursors **26a**,**b**, **29a**,**b**, and **32a**,**b** (Scheme 4). Although the previously described alkylation/acylation approach for the preparation of cyclisation precursors **23a**–**f** was efficient overall, the different reactivities of the aminobromopyridine starting materials **24**, **27**, and **30** did not allow an efficient alkylation/acylation approach to the synthesis of **26a**,**b**, **29a**,**b**, and **32a**,**b**. Preliminary attempts to alkylate starting materials **24** and **27** gave rise to complex mixtures, whereas **30** was largely converted into its quaternary ammonium salt. No attempts were made to optimise the conditions of these reactions, and we decided to turn our full attention to the development of a general approach dealing with all three starting materials **24**, **27**, and **30**. To this end, we proposed an alternate acylation/alkylation approach to the synthesis of tertiary 3- and 4-pyridinamides (Scheme 4). Acylation of the starting material 3-amino-2-bromopyridine **24** with acyl chlorides **16** and **20** at slightly elevated temperature gave secondary 3-pyridinamides **25a** and **25b** in 98 and 94 % yields, respectively. Subsequent methylation of the intermediate secondary amides was carried out with sodium hydride and iodomethane in *N*,*N*-dimethylformamide (DMF), and led to the target tertiary pyridinamides **26a** and **26b** in 91 and 88 % yields, respectively, proving the synthetic utility of an acylation/alkylation approach. Acylation of 3-amino-4-bromopyridine[23] **27** with acyl chlorides **16** and **20** led only to poor yields of secondary 3-pyridinamides **28a** and **28b**. This can be attributed to the strong tendency of 4-halopyridines to undergo nucleophilic aromatic substitution, which leads to a significant amount of unwanted polymerisation of **27**. A similar trend was observed for the subsequent methylation of the intermediate secondary amides, where tertiary pyridinamides **29a** and **29b** were formed in only fair yields.

Thirdly and lastly, the acylation/alkylation approach was implemented for the remaining isomer 4-amino-3-bromopyridine **30**. Not surprisingly, acylation of **30** yielded its corresponding secondary pyridinamides **31a** and **31b** in nearly quantitative yields of 96 and 95 %, respectively. Subsequent methylation of the intermediate secondary amides unfortunately mainly led to the formation of their quaternary pyridinium salts; tertiary pyridinamides **32a** and **32b** were obtained in poor yields.

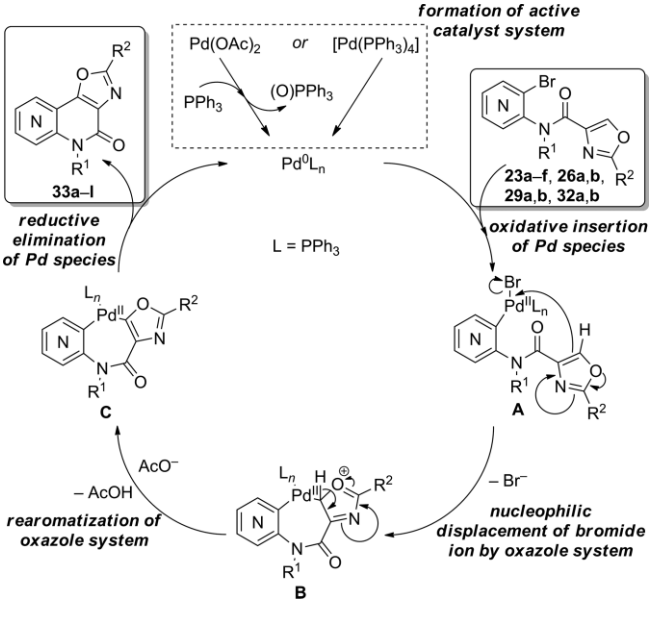
The second key synthetic step in our convergent [3+3] cyclocondensation approach to the synthesis of ONOs **4** is a palladium-catalysed intramolecular C–H arylation, which forms the key heterocycle in the target compounds. Although the literature frequently refers to analogous reactions as Heck reactions,[12] it is assumed that the reaction mechanism leading to Ar–Ar bond construction is noticably different (vide infra).[11] Our initial reaction protocol consisted of heating the cyclisation substrate in *N*,*N*-dimethylacetamide (DMA) at 140 °C for 18 h, using potassium acetate (KOAc) as base and tetrakis(triphenylphosphine)palladium [$Pd(PPh_3)_4$] as catalyst (Scheme 5, conditions [a]). Although this protocol enabled us in most cases to obtain nearly full conversion of starting materials, only products **33g**, **33i**, and **33k** were obtained as pure substances after a

standard chromatographic purification, in 97, 61, and 84 % yields, respectively. All other samples, unfortunately, suffered from contamination by persistent triphenylphosphine oxide (TPPO), which could not be readily removed by standard chromatographic purification. Inspired by the high conversions of starting materials obtained using the initial reaction protocol, we decided to implement a similar immobilised catalyst system, thereby eliminating the need for the removal of TPPO from the solution. The combination of triphenylphosphine resin and palladium acetate [$Pd(OAc)_2$] as a catalyst system caught our attention, since these materials are readily available and should, in situ, form an active catalyst system similar to the previously used [$Pd(PPh_3)_4$]. Our reconsidered reaction protocol involved heating the cyclisation substrate in DMA at 160 °C for 18 h, using KOAc as base and the combination of triphenylphosphine resin and $Pd(OAc)_2$ as catalyst system (Scheme 5, conditions [b]). We were pleased to find that this reaction protocol gave us access to the remaining cyclisation products with excellent purity after standard chromatographic purification. Certain trends were observed for the cyclisation procedure, associated with the regioisomerism of the pyridine incorporated into cyclisation precursors **23**, **26**, **29**, and **32**. 2-Pyridinamides **23** cyclised into tricyclic motifs **33a**–**f** in good to very good yields. Cyclisation precursors **26** gave rise to the corresponding tricyclic motifs **33g**–**h** in very good to excellent yields. For the cyclisation of 3-pyridinamides **29**, the reaction outcome was less consistent, and **33i** and **33j** were formed in 61 and 34 % yields, respectively. A similar observation was made for cyclisation precursors **32**, where phenyl-substituted derivative **33l** was obtained in a significantly lower yield than methylated derivative **33k**. Generally, the cyclisation protocol leading to ONOs **33** tolerates all four possible halopyridine regioisomeric starting materials, as well as diverse substituents on both the oxazole and amide moieties, thus allowing a plethora of points of diversity to be introduced into the final compounds.



Scheme 5. Intramolecular C–H arylation leading to tricyclic scaffolds.

Based on our results and on previous reports in the literature,[11,16] we propose a possible mechanism for the C–H arylation event leading to ONO products **33a**–**l** (Scheme 6). After formation of the active catalyst system (Pd^0L_n), oxidative insertion of the Pd species into the cyclisation precursor C–Br bond gives rise to intermediate **A**. Subsequent nucleophilic displacement of the bromide ion by the oxazole system leads to the formation of oxazolium intermediate **B**, which, in turn, undergoes a base-promoted rearomatisation reaction to give intermediate **C**. Finally, reductive elimination of the Pd species from intermediate **C** yields the desired ONO products **33a**–**l** while regenerating the active catalyst Pd^0L_n. On the basis of this mechanism, we hypothesise that the formation of oxazolium intermediate **B** is the rate-determining step (RDS) in the C–H arylation event leading to ONO products **33a**–**l** (Scheme 6) This hypothesis is consistent with the fact that a relatively high temperature is required for this intramolecular C–H arylation, while the intramolecular C–H arylation of more electron-rich five-membered heterocycles generally proceeds at lower temperatures.[13]



Scheme 6. Proposed mechanism for intramolecular C–H arylation.

Conclusions

A general [3+3] cyclocondensation strategy giving access to the four isomeric [1,3]oxazolo[4,5-*c*]-1-naphthyridin-4(5*H*)-one (ONO) scaffolds has been developed. The first key synthetic step in this strategy is the conversion of *ortho*-aminobromopyridine starting materials into pyridinamide cyclisation precursors through acylation and alkylation, with the order depending on the reactivity of the starting materials. The second key synthetic step involves a palladium-catalysed intramolecular C–H arylation to form the key heterocycle. A reaction mechanism for the C–H arylation event is proposed. This formal [3+3] cyclocondensation strategy tolerates all four possible pyridine regioisomers in the starting materials, and it also allows the introduction of two more points of diversity into the tricyclic condensation products. Three out of the four possible isomeric ONO scaffolds obtained in this work have not been reported previously. Furthermore, C–H arylation of electron-rich azoles has not been systematically investigated previously with all the regioisomers of a halopyridine as cross-coupling partners.

Experimental Section

General Methods: Commercially sourced compounds were used without further purification. Triphenylphosphine resin was 1 % cross-linked with divinylbenzene, triphenylphosphine loading 1.2–1.5 mmol/g, 200–400 mesh. Column chromatography was carried out on silica gel (0.060–0.200 mm, 60 Å). Microwave-assisted experiments were carried out using a CEM Discover microwave reactor and 10 mL sealed reaction vessels. ^{1}H NMR spectra were measured with Bruker Avance 300 (300 MHz), Bruker Ascend 400 (400 MHz), and Bruker Avance II$^+$ 600 (600 MHz) spectrometers. Chemical shifts are reported in δ (ppm) units relative to tetramethylsilane (TMS), which was used as an internal standard. ^{13}C NMR spectra were measured with Bruker Avance 300 (working at 75 MHz), Bruker Ascend 400 (working at 101 MHz), and Bruker Avance II$^+$ 600 (working at 151 MHz) spectrometers. Chemical shifts are reported in δ (ppm) units, and the deuterated solvent was used as an internal standard. Infrared spectra were obtained with a Bruker Alpha-T FTIR spectrometer with a universal sampling module. Melting points were obtained using a Mettler Toledo DSC1 system. High-resolution mass spectra were measured with a Waters Synapt G2 HDMS quadrupole orthogonal-acceleration time-of-flight mass spectrometer. Samples were infused at 3 μL/min, and spectra were obtained in positive (or negative) ionisation mode with a resolution of 15000 (FWHM; full width at half maximum), using leucine enkephalin as lock mass.

Ethyl *N*-{[2-(Benzylamino)pyridin-3-yl]carbonyl}glycinate (9): 2-(Benzylamino)nicotinic acid (**8**; 0.500 g, 2.191 mmol) and triphosgene (0.325 g, 1.095 mmol) were combined in anhydrous 1,4-dioxane (20 mL; 0.110 M) under argon, and the reaction mixture was heated at reflux for 18 h. The mixture was then cooled to room temperature, and ethyl glycinate hydrochloride (0.401 g, 2.88 mmol) and triethylamine (0.401 mL, 2.88 mmol) were added. The reaction mixture was heated at reflux again under argon for 4 h, after which it was cooled to room temperature. The excess of gaseous phosgene was carefully vented for 0.5 h, and then the reaction was quenched with saturated $NaHCO_3$ solution. The mixture was extracted with ethyl acetate (3 ×), the combined organic layers were dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (heptane/ethyl acetate, 7:3) to give compound **9** (273 mg, 53 %) as a white waxy solid. M.p. 57–60 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (s, 1 H), 8.24 (dd, *J* = 4.8, 1.7 Hz, 1 H), 7.67 (dd, *J* = 7.7, 1.8 Hz, 1 H), 7.43–7.18 (m, 5 H), 6.62 (s, 1 H), 6.52 (dd, *J* = 7.7, 4.8 Hz, 1 H), 4.71 (d, *J* = 5.5 Hz, 2 H), 4.25 (q, *J* = 7.1 Hz, 2 H), 4.15 (t, *J* = 5.0 Hz, 2 H), 1.30 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.04, 168.22, 157.84, 152.33, 139.59, 135.50, 128.48, 127.53, 126.91, 110.82, 109.10, 61.77, 44.86, 41.65, 14.15 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1728, 1635, 1574, 1510, 1452, 1412, 1394, 1375, 1364, 1317, 1266, 1223, 1204, 1166, 1085, 1013 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{20}N_3O_3$ [M + H]$^+$ 314.1499; found 314.1497.

1-Benzyl-3,4-dihydro-1*H*-pyrido[2,3-*e*][1,4]diazepine-2,5-dione (11): Ethyl ester **9** (0.797 g, 2.54 mmol) and KOH (0.150 g, 2.67 mmol) were combined in methanol (20 mL; 0.127 M), and the reaction mixture was stirred at 35 °C for 18 h. After this time, the solvent was evaporated under reduced pressure, and the residue was dissolved in acetic acid (12.7 mL; 0.2 M). The reaction mixture was heated at reflux under argon for 48 h, after which the solvent was removed in vacuo. A saturated $NaHCO_3$ solution was added to the residue, and the mixture was extracted with ethyl acetate (3 ×). The combined organic layers were dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (heptane/ethyl acetate gradient, 3:7 → 1:9) to give compound **11** (115 mg, 17 %) as a pale yellow solid. M.p. 200–202 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.61 (dd, *J* = 4.7, 1.9 Hz, 1 H), 8.25 (dd, *J* = 7.7, 1.9 Hz, 1 H), 7.31–7.11 (m, 6 H), 7.01 (s, 1 H), 5.41 (s, 2 H), 3.92 (d, *J* = 6.2 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.51, 167.79, 151.75, 151.00, 140.54, 137.23, 128.44, 127.70, 127.24, 122.73, 120.96, 48.21, 45.59 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1957, 1694, 1666, 1583, 1563, 1495, 1471, 1434, 1395, 1362, 1340, 1298, 1244, 1231, 1205, 1095, 1072, 1040, 1029 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{14}N_3O_2$ [M + H]$^+$ 268.1081; found 268.1076.

5-Benzyl-2-propyl[1,3]oxazolo[4,5-*c*]-1,8-naphthyridin-4(5*H*)-one (12): Diazepine **11** (50 mg, 0.187 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.141 mL, 0.935 mmol), butyric anhydride (0.306 mL, 1.871 mmol), and *o*-xylene (1.50 mL; 0.125 M) were combined in a microwave vessel under argon. The mixture was heated by microwave irradiation at 250 °C for 2 h. The reaction mixture was then concentrated in vacuo. The residue was taken up in CH_2Cl_2 and purified by silica gel chromatography (heptane/ethyl acetate gradient, 9:1 → 5:5) to give compound **12** (21 mg, 35 %) as a pale yellow solid. M.p. 136–138 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.63 (dd, *J* = 4.7, 1.8 Hz, 1 H), 8.17 (dd, *J* = 7.8, 1.8 Hz, 1 H), 7.58–7.47 (m, 2 H), 7.32–7.13 (m, 4 H), 5.87 (s, 2 H), 2.97 (t, *J* = 7.5 Hz, 2 H), 2.03–1.87 (m, 2 H), 1.06 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.28, 157.69, 150.80, 149.36, 148.01, 137.80, 129.96, 129.55, 128.76, 128.19, 127.15, 118.19, 107.24, 44.36, 30.33, 20.38, 13.72 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1683, 1582, 1445, 1391, 1245, 1165, 1131, 1081, 1025 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{18}N_3O_2$ [M + H]$^+$ 320.1394; found 320.1388.

Methyl 2-Methyl-1,3-oxazole-4-carboxylate (14): A stirred mixture of dichloromethane (95 mL) and methanol (10.56 mL) was cooled to 0 °C, after which sodium methoxide solution (30 % in methanol; 0.3 mL) was added. The mixture was stirred at 0 °C for 5 min, and then 2-chloroacetonitrile (12.37 g, 164 mmol) was added in one portion. The resulting mixture was stirred at 0 °C for 1.5 h. After this time, methyl serinate hydrochloride (20.40 g, 131 mmol) was added in one portion, and the reaction mixture was stirred further at room temperature for 18 h. Subsequently, water (40 mL) was added, and the mixture was stirred for 10 min until a clear phase separation was observed. The phases were separated, and

the organic layer was again washed with water (40 mL). The organic layer was concentrated in vacuo, and fresh dichloromethane (100 mL) was added. The reaction mixture was kept at 30 °C, while 1,8-diazabicyclo[5.4.0]undec-7-ene (19.96 g, 131 mmol) was added over 2 h. After the addition was complete, the reaction mixture was washed with HCl (2 M aq.; 40 mL) and water (40 mL). The organic layer was dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (heptane/ethyl acetate, 1:1) to give compound **14** (13.196 g, 71 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16 (s, 1 H), 3.91 (s, 3 H), 2.53 (d, J = 3.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.36, 161.64, 143.75, 133.16, 52.02, 13.75 ppm.

2-Methyl-1,3-oxazole-4-carboxylic Acid (15): Ester **14** (13.148 g, 93 mmol) was dissolved in water (36 mL; 2.59 M). The mixture was stirred vigorously on a water bath (20 °C), and a solution of NaOH (4.472 g, 112 mmol) in water (11 mL) was added dropwise over 15 min. The reaction mixture was stirred further on the water bath (20 °C) for 1 h, after which the mixture was acidified to pH 2 by the dropwise addition of HCl (37 % aq.). The mixture was left unstirred at 0 °C for 1 h, and the resulting precipitate was collected by vacuum filtration. The precipitate was washed with ice-cold water (15 mL) and dried under vacuum to give pure compound **15** (10.654 g, 90 %). ^{1}H NMR (400 MHz, DMSO): δ = 12.96 (s, 1 H), 8.60 (s, 1 H), 2.46 (s, 3 H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 162.06, 161.73, 144.88, 133.12, 13.33 ppm.

Methyl 2-Phenyl-1,3-oxazole-4-carboxylate (18): Methyl serinate hydrochloride (20.0 g, 129 mmol) and potassium carbonate (35.5 g, 257 mmol) were combined in *N*,*N*-dimethylacetamide (320 mL) under nitrogen. Benzaldehyde (13.64 g, 129 mmol) was then added in one portion, and the mixture was stirred at room temperature for 18 h. Subsequently, the reaction mixture was cooled to 0 °C, and bromotrichloromethane (77.0 g, 387 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (58.9 g, 387 mmol) were added. The reaction mixture was stirred at 0 °C for 2 h, then the mixture was stirred further at room temperature for 24 h. The mixture was poured into water (1.2 L), and extracted with diethyl ether (3 ×). The combined organic layers were washed with water and dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (heptane/ethyl acetate gradient, 9:1 → 6:4) to give compound **18** (17.018 g, 65 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.30 (s, 1 H), 8.18–8.04 (m, 2 H), 7.55–7.40 (m, 3 H), 3.96 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.53, 161.81, 143.84, 134.39, 131.25, 128.86, 126.89, 126.35, 52.31 ppm.

2-Phenyl-1,3-oxazole-4-carboxylic Acid (19): Ester **18** (15.0 g, 73.8 mmol) and potassium hydroxide (8.28 g, 148 mmol) were combined in methanol (35 mL; 2.109 M) under nitrogen, and the mixture was stirred at 40 °C for 1 h. Water (120 mL) was then added, and the mixture was acidified to pH 2–3 by the dropwise addition of HCl (37 % aq.). The mixture was extracted with ethyl acetate (3 ×; due to the low solubility of the product a relatively large volume of solvent was required). The combined organic layers were dried with $MgSO_4$, and the solvent was removed under reduced pressure to give compound **19** (12.766 g, 91 %). ^{1}H NMR (300 MHz, DMSO): δ = 13.23 (s, 1 H), 8.88 (s, 1 H), 8.25–7.88 (m, 2 H), 7.71–7.45 (m, 3 H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 161.99, 161.11, 145.39, 134.42, 131.20, 129.22, 126.22, 126.14 ppm.

General Procedure for the Formation of Acyl Chlorides: Carboxylic acid **15** or **19** (6.60 mmol) and dry dichloromethane (21.3 mL; 0.31 M) were combined in a flame-dried flask under nitrogen. The mixture was cooled to 0 °C, and oxalyl chloride (0.867 mL, 9.90 mmol) was added dropwise at 0 °C over 5 min. Stirring was continued at 0 °C for 5 min, and then *N*,*N*-dimethylformamide (0.023 mL, 0.30 mmol) was added as catalyst. The solution was warmed to room temperature, and it was stirred until the mixture no longer effervesced (1–3 h). The solvent was then evaporated, and the resulting acyl chlorides were used immediately for amide coupling reactions. Full conversion of the carboxylic acid starting materials into the corresponding acyl chlorides **16** or **20** was assumed at this point.

General Procedure for the Alkylation of 2-Amino-3-bromopyridine: 2-Amino-3-bromopyridine (**21**; 3.00 g, 17.34 mmol) was dissolved in dry tetrahydrofuran (25.7 mL; 0.674 M) in a flame-dried flask under nitrogen. Sodium hydride (0.479 g, 19.94 mmol) was added quickly in one portion, and the mixture was stirred at 40 °C for 30 min. The mixture was then cooled to 0 °C, and alkyl halide (19.94 mmol) was added dropwise to the mixture while stirring at 0 °C. The reaction mixture was then stirred further at 60 °C for 1 h. After this time, the mixture was cooled to room temperature, and water (50 mL) was added. The mixture was extracted with dichloromethane (3 ×), the combined organic layers were dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography to give pure 2-alkylamino-3-bromopyridines **22**.

3-Bromo-*N*-methylpyridin-2-amine (22a): The adapted general procedure using **21** (3.5 g, 20.23 mmol), with methyl iodide (1.455 mL, 23.26 mmol) as alkyl halide gave, after chromatographic purification (heptane/ethyl acetate, 9:1), **22a** (3.085 g, 82 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08 (dd, J = 4.9, 1.2 Hz, 1 H), 7.56 (dd, J = 7.6, 1.5 Hz, 1 H), 6.41 (dd, J = 7.6, 4.9 Hz, 1 H), 5.06 (s, 1 H), 3.01 (d, J = 4.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.22, 146.72, 139.26, 113.00, 105.63, 28.74 ppm.

3-Bromo-*N*-butylpyridin-2-amine (22b): The general procedure with butyl iodide (2.269 mL, 19.94 mmol) as alkyl halide gave, after chromatographic purification (heptane/ethyl acetate gradient, 10:0 → 9:1), **22b** (3.829 g, 96 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (dd, J = 4.9, 1.5 Hz, 1 H), 7.55 (dd, J = 7.6, 1.6 Hz, 1 H), 6.49–6.28 (m, 1 H), 5.02 (s, 1 H), 3.58–3.32 (m, 2 H), 1.70–1.52 (m, 2 H), 1.51–1.28 (m, 2 H), 0.95 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.70, 146.73, 139.29, 112.88, 105.50, 41.55, 31.70, 20.22, 13.91 ppm.

***N*-Benzyl-3-bromopyridin-2-amine (22c):** The general procedure with benzyl bromide (2.368 mL, 19.94 mmol) as alkyl halide gave, after chromatographic purification (heptane/ethyl acetate, 9:1), **22c** (4.105 g, 90 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06 (dd, J = 4.9, 1.5 Hz, 1 H), 7.58 (dd, J = 7.6, 1.6 Hz, 1 H), 7.40–7.19 (m, 5 H), 6.44 (dd, J = 7.6, 4.9 Hz, 1 H), 5.30 (s, 1 H), 4.66 (d, J = 5.6 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.51, 146.84, 139.64, 139.37, 128.69, 127.66, 127.31, 113.69, 105.58, 45.77 ppm.

General Procedure for the Acylation of 2-(Alkylamino)-3-bromopyridines: Acyl chloride **16** or **20** (6.60 mmol), oven-dried potassium carbonate (1.658 g, 12.00 mmol), 2-(alkylamino)-3-bromopyridine (6.00 mmol), and dry toluene (14 mL) were combined in a flame-dried flask equipped with reflux condenser under nitrogen. (The acyl chloride was used immediately after its preparation, and the flask concerned was reused for this reaction to minimise manipulation of the acyl chloride.) The reaction mixture was heated at reflux (oil bath at 140 °C) for 18 h. After this time, the mixture was cooled to room temperature, and it was diluted with dichloromethane (80 mL). Insoluble solids were removed by filtration, and then washed with dichloromethane. The solvent was removed from the filtrate under reduced pressure, and the residue was purified by silica gel chromatography to give the tertiary 2-pyridinamides **23**.

***N*-(3-Bromopyridin-2-yl)-*N*,2-dimethyl-1,3-oxazole-4-carboxamide (23a):** The general procedure with 2-(alkylamino)-3-bromopyridine **22a** and acyl chloride **16** gave, after chromatographic purification (heptane/ethyl acetate gradient, 4:6 → 3:7), **23a** (1.277 g, 72 %) as a white solid. M.p. 120–122 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.47 (dd, *J* = 4.7, 1.6 Hz, 1 H), 7.96 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.60 (s, 1 H), 7.21 (dd, *J* = 7.9, 4.7 Hz, 1 H), 3.42 (s, 3 H), 2.25 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.57, 160.50, 154.62, 147.86, 142.26, 142.06, 136.14, 124.45, 119.87, 35.22, 13.66 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1639, 1581, 1566, 1415, 1370, 1316, 1303, 1241, 1189, 1113, 1069, 1037, 1020 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{11}BrN_3O_2$ $[M + H]^+$ 296.0029; found 296.0034.

***N*-(3-Bromopyridin-2-yl)-*N*-methyl-2-phenyl-1,3-oxazole-4-carboxamide (23b):** The general procedure with 2-(alkylamino)-3-bromopyridine **22a** and acyl chloride **20** gave, after chromatographic purification (heptane/ethyl acetate, 5:5), **23b** (1.777 g, 83 %) as a pale brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (dd, *J* = 4.7, 1.6 Hz, 1 H), 8.04 (s, 1 H), 7.99 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.64 (s, 2 H), 7.44–7.31 (m, 3 H), 7.23 (dd, *J* = 7.9, 4.7 Hz, 1 H), 3.46 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.36, 160.32, 154.83, 147.79, 142.78, 142.05, 137.45, 130.63, 128.63, 126.71, 126.31, 124.38, 120.07, 35.18 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1645, 1565, 1483, 1415, 1366, 1332, 1286, 1266, 1203, 1112, 1070, 1057, 1021 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{13}BrN_3O_2$ $[M + H]^+$ 358.0186; found 358.0193.

***N*-(3-Bromopyridin-2-yl)-*N*-butyl-2-methyl-1,3-oxazole-4-carboxamide (23c):** The general procedure with 2-(alkylamino)-3-bromopyridine **22b** and acyl chloride **16** gave, after chromatographic purification (heptane/ethyl acetate gradient, 4:6 → 3:7), **23c** (1.700 g, 84 %) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.50 (dd, *J* = 4.7, 1.7 Hz, 1 H), 7.93 (dd, *J* = 7.9, 1.6 Hz, 1 H), 7.52 (s, 1 H), 7.20 (dd, *J* = 7.9, 4.7 Hz, 1 H), 4.06 (s, 1 H), 3.71 (s, 1 H), 2.23 (s, 3 H), 1.81–1.54 (m, 2 H), 1.47–1.24 (m, 2 H), 0.90 (t, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.25, 160.41, 153.80, 147.69, 142.16, 141.80, 136.45, 124.17, 120.71, 48.56, 29.78, 20.25, 13.79, 13.61 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1643, 1587, 1567, 1430, 1394, 1329, 1304, 1219, 1183, 1140, 1109, 1080, 1021 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{17}BrN_3O_2$ $[M + H]^+$ 338.0499; found 338.0491.

***N*-(3-Bromopyridin-2-yl)-*N*-butyl-2-phenyl-1,3-oxazole-4-carboxamide (23d):** The general procedure with 2-(alkylamino)-3-bromopyridine **22b** and acyl chloride **20** gave, after chromatographic purification (heptane/ethyl acetate, 8:2), **23d** (1.234 g, 93 %) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (dd, *J* = 4.7, 1.6 Hz, 1 H), 8.03–7.93 (m, 2 H), 7.70–7.60 (m, 2 H), 7.43–7.29 (m, 3 H), 7.21 (dd, *J* = 7.9, 4.7 Hz, 1 H), 4.21–4.03 (m, 1 H), 3.89–3.70 (m, 1 H), 1.81–1.61 (m, 2 H), 1.49–1.33 (m, 2 H), 0.93 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.03, 160.21, 154.04, 147.64, 142.69, 142.00, 137.79, 130.60, 128.63, 126.77, 126.34, 124.08, 120.92, 48.63, 29.79, 20.34, 13.84 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1644, 1564, 1486, 1429, 1392, 1328, 1286, 1263, 1227, 1188, 1112, 1079, 1057, 1022 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{19}BrN_3O_2$ $[M + H]^+$ 400.0655; found 400.0651.

***N*-Benzyl-*N*-(3-bromopyridin-2-yl)-2-methyl-1,3-oxazole-4-carboxamide (23e):** The general procedure with 2-(alkylamino)-3-bromopyridine **22c** and acyl chloride **16** gave, after chromatographic purification (heptane/ethyl acetate gradient, 6:4 → 5:5), **23e** (1.303 g, 58 %) as a white solid. M.p. 122–125 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 (dd, *J* = 4.6, 1.4 Hz, 1 H), 7.80 (d, *J* = 7.9 Hz, 1 H), 7.58 (s, 1 H), 7.39–7.30 (m, 2 H), 7.28–7.17 (m, 3 H), 7.10 (dd, *J* = 7.9, 4.7 Hz, 1 H), 5.16 (s, *J* = 33.8 Hz, 2 H), 2.23 (s, *J* = 26.9 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.44, 160.50, 153.42, 147.61, 142.19, 142.07, 136.44, 136.20, 129.24, 128.17, 127.45, 124.01, 120.85, 52.00, 13.65 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1642, 1587, 1567, 1496, 1457, 1425, 1390, 1377, 1354, 1331, 1308, 1240, 1226, 1184, 1117, 1090, 1078, 1028, 1015 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{15}BrN_3O_2$ $[M + H]^+$ 372.0342; found 372.0333.

***N*-Benzyl-*N*-(3-bromopyridin-2-yl)-2-phenyl-1,3-oxazole-4-carboxamide (23f):** The general procedure with 2-(alkylamino)-3-bromopyridine **22c** and acyl chloride **20** gave, after chromatographic purification (heptane/ethyl acetate, 8:2), **23f** (2.277 g, 87 %) as a pale yellow solid. M.p. 135–138 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (d, *J* = 4.5 Hz, 1 H), 8.00 (s, 1 H), 7.84 (d, *J* = 7.9 Hz, 1 H), 7.69–7.61 (m, 2 H), 7.50–7.09 (m, 9 H), 5.20 (s, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.24, 160.35, 153.62, 147.60, 142.97, 141.99, 137.70, 136.19, 130.70, 129.33, 128.68, 128.24, 127.53, 126.73, 126.41, 124.04, 121.04, 52.12 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1670, 1605, 1558, 1494, 1450, 1427, 1382, 1354, 1326, 1303, 1261, 1243, 1200, 1185, 1134, 1119, 1059, 1024 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{17}BrN_3O_2$ $[M + H]^+$ 434.0499; found 434.0477.

General Procedure for the Acylation of 3- and 4-Aminopyridines: Acyl chloride **16** or **20** (6.60 mmol) and dry tetrahydrofuran (5 mL or 10 mL) were combined in a flame-dried flask under nitrogen. (The acyl chloride was used immediately after its preparation, and the flask concerned was reused for this reaction to minimise manipulation of the acyl chloride.) The mixture was cooled to 0 °C, and dry *N*,*N*-diisopropylethylamine (4.19 mL, 24.00 mmol) was added dropwise. Next, the aminobromopyridine (1.038 g, 6 mmol) was added in one portion. The reaction mixture was stirred first at 0 °C for 5 min, and then at 40 °C for 18 h. After this time, the mixture was cooled to room temperatue. The reaction mixture was dried with $MgSO_4$ to ensure precipitation of HCl salts, and then insoluble solids were removed by filtration, and washed with dry tetrahydrofuran. The solvent was removed from the filtrate under reduced pressure, and the residue was purified by silica gel chromatography to give the secondary pyridinamides.

***N*-(2-Bromopyridin-3-yl)-2-methyl-1,3-oxazole-4-carboxamide (25a):** The general procedure with 3-amino-2-bromopyridine **24** and acyl chloride **16** in tetrahydrofuran (5 mL) gave, after chromatographic purification (heptane/ethyl acetate, 5:5), **25a** (1.658 g, 98 %) as a white solid. M.p. 176–178 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.34 (s, 1 H), 8.82 (dd, *J* = 8.1, 1.8 Hz, 1 H), 8.21 (s, 1 H), 8.13 (dd, *J* = 4.6, 1.8 Hz, 1 H), 7.31 (dd, *J* = 8.1, 4.6 Hz, 1 H), 2.55 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.77, 159.07, 144.58, 141.81, 135.83, 133.50, 133.28, 128.35, 123.50, 13.90 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1687, 1592, 1575, 1559, 1504, 1452, 1373, 1310, 1298, 1216, 1199, 1174, 1121, 1095, 1064, 1049 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_9BrN_3O_2$ $[M + H]^+$ 281.9873; found 281.9886.

***N*-(2-Bromopyridin-3-yl)-2-phenyl-1,3-oxazole-4-carboxamide (25b):** The general procedure with 3-amino-2-bromopyridine **24** and acyl chloride **20** in tetrahydrofuran (5 mL) gave, after chromatographic purification (heptane/ethyl acetate gradient, 7:3 → 6:4), **25b** (1.946 g, 94 %) as a white solid. M.p. 179–181 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.54 (s, 1 H), 8.88–8.78 (m, 1 H), 8.38–8.29 (m, 1 H), 8.17–8.02 (m, 3 H), 7.57–7.44 (m, 3 H), 7.36–7.23 (m, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.70, 158.95, 144.60, 141.67, 136.84, 133.48, 133.29, 131.40, 128.98, 128.24, 128.21, 126.77, 126.14, 123.54 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1670, 1581, 1557, 1512, 1449, 1385, 1337, 1305, 1263, 1198, 1112, 1061, 1048, 1023, 1000 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{11}BrN_3O_2$ $[M + H]^+$ 344.0029; found 344.0027.

***N*-(4-Bromopyridin-3-yl)-2-methyl-1,3-oxazole-4-carboxamide (28a):** The general procedure with 3-amino-4-bromopyridine hydrochloride **27**, dry *N*,*N*-diisopropylethylamine (5.24 mL, 30.00 mmol), and acyl chloride **16** in tetrahydrofuran (10 mL) gave, after chromat-

ographic purification (heptane/ethyl acetate, 7:3), **28a** (215 mg, 13 %) as a pale brown solid. M.p. 155–157 °C. An additional 1 equiv. of *N*,*N*-diisopropylethylamine (24.00 mmol + 6.00 mmol) was used to compensate for the use of a hydrochloride salt as starting material. ^{1}H NMR (400 MHz, $CDCl_3$, 85:15 mixture of rotamers): major rotamer: δ = 9.73 (s, 1 H), 9.18 (s, 1 H), 8.31 (d, *J* = 5.2 Hz, 1 H), 8.22 (s, 1 H), 7.37 (d, *J* = 5.2 Hz, 1 H), 2.54 (s, 3 H) ppm; minor rotamer: δ = 9.68 (s, 1 H), 9.18 (s, 1 H), 8.22 (s, 1 H), 8.20 (s, 1 H), 7.54 (d, *J* = 8.7 Hz, 1 H), 2.54 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, both rotamers): δ = 161.74, 158.45, 145.45, 145.39, 143.16, 143.13, 141.96, 135.74, 133.23, 132.32, 131.94, 127.31, 123.97, 123.24, 13.86 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1706, 1597, 1577, 1516, 1457, 1414, 1378, 1314, 1226, 1097 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_9BrN_3O_2$ $[M + H]^+$ 281.9873; found 281.9864.

***N*-(4-Bromopyridin-3-yl)-2-phenyl-1,3-oxazole-4-carboxamide (28b):** The general procedure with 3-amino-4-bromopyridine hydrochloride **27**, dry *N*,*N*-diisopropylethylamine (5.24 mL, 30.00 mmol), and acyl chloride **20** in tetrahydrofuran (10 mL) gave, after chromatographic purification (heptane/ethyl acetate, 6:4), **28b** (247 mg, 12 %) as a pale brown solid. M.p. 189–191 °C. An additional 1 mol-equiv. of *N*,*N*-diisopropylethylamine (24.00 mmol + 6.00 mmol) was used to compensate for the use of a hydrochloride salt as starting material. ^{1}H NMR (400 MHz, $CDCl_3$, 9:1 mixture of rotamers): major rotamer: δ = 9.77 (s, 1 H), 9.37 (s, 1 H), 8.44–8.35 (m, 1 H), 8.33 (d, *J* = 5.2 Hz, 1 H), 8.12–8.07 (m, 2 H), 7.62–7.36 (m, 4 H) ppm; minor rotamer: δ = 9.72 (s, 1 H), 9.37 (s, 1 H), 8.44–8.35 (m, 1 H), 8.33 (d, *J* = 5.2 Hz, 1 H), 8.22 (d, *J* = 5.2 Hz, 1 H), 8.12–8.07 (m, 2 H), 7.62–7.36 (m, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, both rotamers): δ = 161.75, 158.39, 145.45, 143.10, 141.91, 136.78, 132.38, 131.93, 131.44, 129.00, 127.35, 126.80, 126.19, 124.02, 123.28 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1711, 1590, 1562, 1523, 1487, 1450, 1419, 1337, 1311, 1259, 1224, 1148, 1103, 1076, 1058, 1028, 1002 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{11}BrN_3O_2$ $[M + H]^+$ 344.0029; found 344.0033.

***N*-(3-Bromopyridin-4-yl)-2-methyl-1,3-oxazole-4-carboxamide (31a):** The general procedure with 4-amino-3-bromopyridine **30** and acyl chloride **16** in tetrahydrofuran (10 mL) gave, after chromatographic purification (heptane/ethyl acetate, 5:5), **31a** (1.619 g, 96 %) as a white solid. M.p. 151–153 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.48 (s, 1 H), 8.68 (s, 1 H), 8.51 (d, *J* = 5.6 Hz, 1 H), 8.46 (d, *J* = 5.6 Hz, 1 H), 8.23 (s, 1 H), 2.55 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.82, 159.09, 151.81, 149.67, 142.25, 142.22, 135.68, 114.58, 110.79, 13.88 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1702, 1596, 1574, 1502, 1453, 1402, 1380, 1315, 1305, 1269, 1226, 1217, 1180, 1137, 1091, 1081, 1018 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_9BrN_3O_2$ $[M + H]^+$ 281.9873; found 281.9874.

***N*-(3-Bromopyridin-4-yl)-2-phenyl-1,3-oxazole-4-carboxamide (31b):** The general procedure with 4-amino-3-bromopyridine **30** and acyl chloride **20** in tetrahydrofuran (10 mL) gave, after chromatographic purification (heptane/ethyl acetate, 5:5), **31b** (1.969 g, 95 %) as a white solid. M.p. 146–148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.67 (s, 1 H), 8.69 (s, 1 H), 8.52 (d, *J* = 5.5 Hz, 1 H), 8.47 (d, *J* = 5.5 Hz, 1 H), 8.36 (d, *J* = 4.3 Hz, 1 H), 8.15–8.02 (m, 2 H), 7.58–7.46 (m, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 161.78, 159.00, 151.83, 149.73, 142.22, 142.08, 136.71, 131.52, 129.01, 126.80, 126.05, 114.53, 110.84 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1699, 1576, 1559, 1507, 1450, 1407, 1336, 1313, 1253, 1181, 1145, 1098, 1058, 1020, 1002 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{11}BrN_3O_2$ $[M + H]^+$ 344.0029; found 344.0031.

General Procedure for the Methylation of Secondary 3- and 4-Pyridinamides: The secondary pyridinamide (2.00 mmol) and dry *N*,*N*-dimethylformamide (6.00 mL; 0.33 M) were combined in a flame-dried flask under nitrogen. The mixture was cooled to 0 °C, and sodium hydride (0.058 g, 2.40 mmol) was added in one portion to the mixture at 0 °C. Stirring was continued at 0 °C for 20 min, and then methyl iodide (0.138 mL, 2.20 mmol) was added dropwise. The reaction mixture was stirred further at 0 °C for 30 min, then it was warmed to room temperature and stirred at room temperature for 18 h. Next, water (60 mL) was added, and the mixture was extracted with dichloromethane (3 ×). The combined organic layers were dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography to give the tertiary pyridinamides.

***N*-(2-Bromopyridin-3-yl)-*N*,2-dimethyl-1,3-oxazole-4-carboxamide (26a):** The general procedure using **25a** gave, after chromatographic purification (heptane/ethyl acetate gradient, 4:6 → 8:2), **26a** (0.496 g, 84 %) as a pale pink solid. M.p. 133–135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38 (dd, *J* = 4.7, 1.8 Hz, 1 H), 7.68–7.55 (m, 2 H), 7.34 (dd, *J* = 7.7, 4.7 Hz, 1 H), 3.37 (s, 3 H), 2.23 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.52, 160.62, 149.02, 143.36, 142.27, 140.59, 138.12, 135.79, 123.44, 36.89, 13.64 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1634, 1581, 1562, 1466, 1444, 1420, 1400, 1381, 1317, 1304, 1236, 1194, 1116, 1070, 1049, 1021 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{11}BrN_3O_2$ $[M + H]^+$ 296.0029; found 296.0026.

***N*-(2-Bromopyridin-3-yl)-*N*-methyl-2-phenyl-1,3-oxazole-4-carboxamide (26b):** The adapted general procedure using **25b** (1.377 g, 4.00 mmol) gave, after chromatographic purification (heptane/ethyl acetate, 6:4), **26b** (1.264 g, 88 %) as a white solid. M.p. 139–143 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (dd, *J* = 4.7, 1.8 Hz, 1 H), 8.06 (s, 1 H), 7.65 (dd, *J* = 7.7, 1.7 Hz, 3 H), 7.43–7.30 (m, 4 H), 3.41 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.23, 160.49, 148.87, 143.73, 143.10, 140.78, 137.99, 137.07, 130.77, 128.72, 126.56, 126.37, 123.34, 36.89 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1638, 1557, 1488, 1451, 1401, 1373, 1320, 1286, 1263, 1204, 1118, 1054, 1024 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{13}BrN_3O_2$ $[M + H]^+$ 358.0186; found 358.0180.

***N*-(4-Bromopyridin-3-yl)-*N*,2-dimethyl-1,3-oxazole-4-carboxamide (29a):** The adapted general procedure using **28a** (0.200 g, 0.709 mmol) gave, after chromatographic purification (heptane/ethyl acetate, 2:8), **29a** (0.110 g, 52 %) as a pale brown solid. M.p. 102–104 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 8:2 mixture of rotamers): major rotamer: δ = 8.54–8.42 (m, 2 H), 7.66–7.51 (m, 1 H), 7.43 (d, *J* = 5.2 Hz, 1 H), 3.38 (s, 3 H), 2.22 (s, 3 H); ppm; minor rotamer: δ = 8.54–8.42 (m, 1 H), 8.39 (d, *J* = 5.3 Hz, 1 H), 7.66–7.51 (m, 2 H), 3.38 (s, 3 H), 2.22 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, both rotamers): δ = 161.78, 160.66, 150.78, 150.64, 149.59, 149.41, 142.63, 142.20, 138.63, 135.68, 133.63, 128.16, 124.93, 37.00, 13.63 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1643, 1585, 1556, 1477, 1405, 1370, 1324, 1305, 1268, 1235, 1191, 1111, 1083 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{11}BrN_3O_2$ $[M + H]^+$ 296.0029; found 296.0026.

***N*-(4-Bromopyridin-3-yl)-*N*-methyl-2-phenyl-1,3-oxazole-4-carboxamide (29b):** The adapted general procedure using **28b** (0.202 g, 0.587 mmol) gave, after chromatographic purification (heptane/ethyl acetate, 2:8), **29b** (0.130 g, 62 %) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 9:1 mixture of rotamers): δ = 8.61–8.54 (m, 1 H), 8.52 (d, *J* = 5.3 Hz, 1 H), 8.41 (d, *J* = 5.3 Hz, 1 H), 8.09–8.01 (m, 1 H), 7.64 (t, *J* = 6.4 Hz, 2 H), 7.49–7.30 (m, 4 H), 3.43 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, both rotamers): δ = 161.59, 160.51, 151.01, 149.55, 149.33, 143.05, 142.73, 138.79, 137.03, 130.77, 128.71, 126.59, 126.38, 124.74, 37.09 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1638, 1556, 1481, 1448, 1432, 1404, 1377, 1331, 1286, 1256, 1200, 1121, 1087, 1057, 1024 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{13}BrN_3O_2$ $[M + H]^+$ 358.0186; found 358.0175.

***N*-(3-Bromopyridin-4-yl)-*N*,2-dimethyl-1,3-oxazole-4-carboxamide (32a):** The general procedure using **31a** gave, after chromatographic purification (heptane/ethyl acetate, 2:8), **32a** (0.096 g, 16 %) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.80 (s, 1 H), 8.55 (d, J = 5.1 Hz, 1 H), 7.69 (s, 1 H), 7.23 (d, J = 5.1 Hz, 1 H), 3.39 (s, 3 H), 2.27 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.22, 160.71, 153.40, 150.55, 149.77, 142.39, 135.74, 124.61, 121.20, 36.87, 13.68 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1642, 1587, 1566, 1485, 1423, 1402, 1365, 1324, 1307, 1282, 1237, 1200, 1172, 1110, 1084, 1039, 1021 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{11}BrN_3O_2$ [M + H]$^+$ 296.0029; found 296.0034.

***N*-(3-Bromopyridin-4-yl)-*N*-methyl-2-phenyl-1,3-oxazole-4-carboxamide (32b):** The adapted general procedure using **31b** (1.377 g, 4.00 mmol) gave, after chromatographic purification (heptane/ethyl acetate, 5:5), **32b** (0.209 g, 15 %) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.84 (s, 1 H), 8.59 (d, J = 5.1 Hz, 1 H), 8.09 (s, 1 H), 7.64 (s, 2 H), 7.50–7.32 (m, 3 H), 7.30 (d, J = 5.1 Hz, 1 H), 3.42 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.92, 160.60, 153.21, 150.72, 149.68, 143.13, 136.99, 130.86, 128.80, 126.50, 126.39, 124.70, 121.57, 36.78 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1645, 1561, 1481, 1449, 1422, 1399, 1367, 1332, 1260, 1205, 1175, 1112, 1080, 1057, 1022 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{13}BrN_3O_2$ [M + H]$^+$ 358.0186; found 358.185.

General Procedure for Intramolecular C–H Arylation To Give Tricyclic Scaffolds

Conditions [a]: Bromopyridine (1.00 mmol), $[Pd(PPh_3)_4]$ (0.05 mmol), and KOAc (1.50 mmol) were combined in DMA (7 mL; 0.143 M), and the mixture was stirred under nitrogen at 140 °C for 18 h. The reaction mixture was then concentrated in vacuo. The residue was suspended in CH_2Cl_2 and purified by silica gel chromatography to give products **33**.

Conditions [b]: Bromopyridine (1.00 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_3 resin (83 mg, corresponding to a PPh_3 loading of 0.10–0.13 mmol), and KOAc (1.50 mmol) were combined in *N*,*N*-dimethylacetamide (7 mL; 0.143 M), and the mixture was stirred under nitrogen at 160 °C for 18 h. The reaction mixture was then concentrated in vacuo. The residue was suspended in dichloromethane and purified by silica gel chromatography to give products **33**.

2,5-Dimethyl[1,3]oxazolo[4,5-*c*]-1,8-naphthyridin-4(5*H*)-one (33a): The general procedure (conditions [b]) gave, after chromatographic purification (dichloromethane/diethyl ether, 92:8), **33a** (110 mg, 73 %) as a white solid. M.p. 218–219 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.66 (dd, J = 4.7, 1.8 Hz, 1 H), 8.18 (dd, J = 7.8, 1.8 Hz, 1 H), 7.29 (dd, J = 7.8, 4.8 Hz, 1 H), 3.92 (s, 3 H), 2.72 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.75, 157.70, 150.79, 149.34, 148.30, 129.92, 129.45, 118.05, 107.03, 28.86, 14.32 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1671, 1581, 1440, 1377, 1349, 1324, 1309, 1263, 1233, 1212, 1134, 1104, 1063, 1022, 1009 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{10}N_3O_2$ [M + H]$^+$ 216.0768; found 216.0770.

5-Methyl-2-phenyl[1,3]oxazolo[4,5-*c*]-1,8-naphthyridin-4(5*H*)-one (33b): The general procedure (conditions [b]) gave, after chromatographic purification (dichloromethane/diethyl ether, 9:1), **33b** (232 mg, 84 %) as a pale orange solid. M.p. 268–270 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.69 (dd, J = 4.7, 1.8 Hz, 1 H), 8.36–8.23 (m, 3 H), 7.60–7.48 (m, 3 H), 7.33 (dd, J = 7.8, 4.7 Hz, 1 H), 3.97 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.40, 157.97, 150.57, 149.55, 148.53, 131.84, 131.02, 129.66, 129.02, 127.49, 126.15, 118.18, 107.11, 29.04 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1673, 1575, 1557, 1498, 1480, 1447, 1385, 1351, 1333, 1285, 1259, 1218, 1150, 1109, 1067, 1050, 1023 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{12}N_3O_2$ [M + H]$^+$ 278.0924; found 278.0933.

5-Butyl-2-methyl[1,3]oxazolo[4,5-*c*]-1,8-naphthyridin-4(5*H*)-one (33c): The general procedure (conditions [b]) gave, after chromatographic purification (dichloromethane/diethyl ether, 95:5), **33c** (195 mg, 76 %) as a white solid. M.p. 149–152 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.65 (dd, J = 4.7, 1.9 Hz, 1 H), 8.17 (dd, J = 7.8, 1.9 Hz, 1 H), 7.27 (dd, J = 7.8, 4.7 Hz, 1 H), 4.65–4.57 (m, 2 H), 2.71 (s, J = 4.0 Hz, 3 H), 1.81–1.67 (m, 2 H), 1.54–1.36 (m, 2 H), 0.96 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.61, 157.28, 150.70, 149.38, 147.92, 129.90, 129.37, 117.89, 106.93, 41.47, 30.35, 20.23, 14.28, 13.90 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1672, 1589, 1578, 1556, 1486, 1437, 1393, 1375, 1346, 1304, 1283, 1267, 1236, 1187, 1118, 1105, 1064, 1035, 1003 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{16}N_3O_2$ [M + H]$^+$ 258.1237; found 258.1237.

5-Butyl-2-phenyl[1,3]oxazolo[4,5-*c*]-1,8-naphthyridin-4(5*H*)-one (33d): The general procedure (conditions [b]) gave, after chromatographic purification (dichloromethane/diethyl ether, 9:1), **33d** (267 mg, 84 %) as a white solid. M.p. 151–152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.67 (dd, J = 4.7, 1.8 Hz, 1 H), 8.32–8.24 (m, 3 H), 7.57–7.48 (m, 3 H), 7.30 (dd, J = 7.8, 4.7 Hz, 1 H), 4.80–4.55 (m, 2 H), 1.83–1.69 (m, 2 H), 1.59–1.37 (m, 2 H), 0.98 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.28, 157.58, 150.49, 149.60, 148.16, 131.77, 130.99, 129.60, 129.00, 127.44, 126.19, 118.02, 107.04, 41.62, 30.40, 20.27, 13.96 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1685, 1587, 1574, 1556, 1493, 1441, 1390, 1371, 1346, 1317, 1303, 1283, 1254, 1232, 1191, 1148, 1124, 1066, 1024 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{18}N_3O_2$ [M + H]$^+$ 320.1394; found 320.1389.

5-Benzyl-2-methyl[1,3]oxazolo[4,5-*c*]-1,8-naphthyridin-4(5*H*)-one (33e): The general procedure (conditions [b]) gave, after chromatographic purification (dichloromethane/diethyl ether, 95:5), **33e** (245 mg, 84 %) as a white solid. M.p. 172–175 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.62 (dd, J = 4.7, 1.8 Hz, 1 H), 8.13 (dd, J = 7.8, 1.8 Hz, 1 H), 7.54–7.46 (m, 2 H), 7.28–7.13 (m, 4 H), 5.85 (s, 2 H), 2.70 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.81, 157.53, 150.97, 149.42, 147.95, 137.76, 130.02, 129.51, 128.70, 128.19, 127.16, 118.27, 107.09, 44.35, 14.33 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1681, 1580, 1550, 1495, 1484, 1438, 1407, 1386, 1375, 1350, 1305, 1269, 1258, 1224, 1173, 1130, 1108, 1069, 1028, 1009 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{14}N_3O_2$ [M + H]$^+$ 292.1081; found 292.1086.

5-Benzyl-2-phenyl[1,3]oxazolo[4,5-*c*]-1,8-naphthyridin-4(5*H*)-one (33f): The general procedure (conditions [b]) gave, after chromatographic purification (dichloromethane/diethyl ether, 95:5), **33f** (315 mg, 89 %) as a white solid. M.p. 232–235 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.63 (dd, J = 4.7, 1.8 Hz, 1 H), 8.32–8.18 (m, 3 H), 7.60–7.42 (m, 5 H), 7.31–7.14 (m, 4 H), 5.87 (s, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.37, 157.74, 150.66, 149.56, 148.06, 137.70, 131.80, 131.01, 129.66, 128.99, 128.85, 128.20, 127.40, 127.23, 126.05, 118.35, 107.10, 44.41 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1680, 1606, 1577, 1556, 1495, 1440, 1389, 1348, 1321, 1300, 1280, 1255, 1243, 1160, 1136, 1107, 1079, 1055, 1024 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{16}N_3O_2$ [M + H]$^+$ 354.1237; found 354.1228.

2,5-Dimethyl[1,3]oxazolo[4,5-*c*]-1,5-naphthyridin-4(5*H*)-one (33g): The general procedure (conditions [a]) gave, after chromatographic purification (dichloromethane/diethyl ether, 8:2 until the triphenylphosphine oxide was removed, then dichloromethane/methanol, 97:3), **33g** (208 mg, 97 %) as a pale yellow solid. M.p. 242–243 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.63 (d, J = 4.4 Hz, 1 H), 7.83 (d, J = 8.7 Hz, 1 H), 7.56 (dd, J = 8.6, 4.5 Hz, 1 H), 3.83 (s, 3 H), 2.75 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.63, 156.79, 151.54, 144.63, 135.02, 132.54, 129.48, 124.13, 122.56, 29.41, 14.32 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1670, 1626, 1581, 1494, 1461, 1398, 1382, 1354, 1316, 1271, 1235, 1213, 1113, 1053 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{10}N_3O_2$ [M + H]$^+$ 216.0768; found 216.0747.

5-Methyl-2-phenyl[1,3]oxazolo[4,5-*c*]-1,5-naphthyridin-4(5*H*)-one (33h): The general procedure (conditions [b]) gave, after chromatographic purification (dichloromethane/diethyl ether, 8:2), **33h** (246 mg, 89 %) as a pale yellow solid. M.p. >300 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.67 (dd, *J* = 4.5, 1.2 Hz, 1 H), 8.43–8.36 (m, 2 H), 7.85 (dd, *J* = 8.7, 1.2 Hz, 1 H), 7.62–7.48 (m, 4 H), 3.86 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.09, 157.00, 151.26, 144.76, 135.24, 133.54, 132.02, 129.48, 128.99, 127.86, 125.98, 124.21, 122.62, 29.54 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1669, 1620, 1572, 1552, 1496, 1478, 1446, 1398, 1355, 1332, 1272, 1261, 1219, 1119, 1071, 1052, 1018 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{12}N_3O_2$ $[M + H]^+$ 278.0924; found 278.0951.

2,5-Dimethyl[1,3]oxazolo[4,5-*c*]-1,7-naphthyridin-4(5*H*)-one (33i): The adapted general procedure (conditions [a]) on **29a** (92 mg, 0.311 mmol) gave, after chromatographic purification (dichloromethane/diethyl ether, 8:2 until the triphenylphosphine oxide was removed, then dichloromethane/methanol, 96:4), **33i** (41 mg, 61 %) as a white solid. M.p. 238–240 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.96 (s, 1 H), 8.58 (d, *J* = 5.1 Hz, 1 H), 7.75 (dd, *J* = 5.1, 0.6 Hz, 1 H), 3.91 (s, 3 H), 2.75 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.83, 156.76, 150.39, 142.74, 137.71, 133.25, 132.79, 116.44, 113.94, 29.39, 14.41 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1679, 1641, 1575, 1508, 1420, 1379, 1351, 1333, 1310, 1256, 1235, 1173, 1127, 1105, 1059, 1034 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{10}N_3O_2$ $[M + H]^+$ 216.0768; found 216.0762.

5-Methyl-2-phenyl[1,3]oxazolo[4,5-*c*]-1,7-naphthyridin-4(5*H*)-one (33j): The adapted general procedure (conditions [b]) on **29b** (100 mg, 0.279 mmol) gave, after chromatographic purification (dichloromethane/diethyl ether, 1:1), **33j** (26 mg, 34 %) as a white solid. M.p. 233–234 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.99 (s, 1 H), 8.62 (d, *J* = 5.1 Hz, 1 H), 8.35–8.30 (m, 2 H), 7.88 (d, *J* = 5.1 Hz, 1 H), 7.64–7.51 (m, 3 H), 3.95 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.34, 157.00, 150.11, 142.84, 137.78, 133.81, 133.37, 132.26, 129.13, 127.75, 125.86, 116.48, 114.04, 29.53 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1682, 1637, 1603, 1585, 1552, 1504, 1480, 1448, 1420, 1357, 1323, 1309, 1236, 1174, 1140, 1109, 1076, 1057, 1016 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{12}N_3O_2$ $[M + H]^+$ 278.0924; found 278.0923.

2,5-Dimethyl[1,3]oxazolo[4,5-*c*]-1,6-naphthyridin-4(5*H*)-one (33k): The adapted general procedure (conditions [a]) on **32a** (92 mg, 0.311 mmol) gave, after chromatographic purification (dichloromethane/diethyl ether, 5:5 until the triphenylphosphine oxide was removed, then dichloromethane/methanol, 9:1), **33k** (79 mg, 84 %) as a white solid. M.p. 272–273 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.15 (s, 1 H), 8.69 (d, *J* = 5.9 Hz, 1 H), 7.33 (d, *J* = 6.1 Hz, 1 H), 3.79 (s, 3 H), 2.74 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.86, 157.40, 150.89, 149.66, 144.08, 142.89, 130.05, 109.32, 107.89, 29.42, 14.30 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1671, 1584, 1567, 1503, 1427, 1403, 1379, 1317, 1220, 1188, 1112, 1025, 1008 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{10}N_3O_2$ $[M + H]^+$ 216.0768; found 216.0793.

5-Methyl-2-phenyl[1,3]oxazolo[4,5-*c*]-1,6-naphthyridin-4(5*H*)-one (33l): The adapted general procedure (conditions [b]) on **32b** (162 mg, 0.452 mmol) gave, after chromatographic purification (dichloromethane/diethyl ether, 8:2), **33l** (68 mg, 54 %) as a white solid. M.p. >300 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.28 (s, 1 H), 8.71 (d, *J* = 6.1 Hz, 1 H), 8.41–8.23 (m, 2 H), 7.64–7.49 (m, 3 H), 7.36 (d, *J* = 6.0 Hz, 1 H), 3.83 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.50, 157.65, 150.65, 149.82, 144.26, 143.06, 132.04, 131.10, 129.09, 127.60, 125.91, 109.39, 107.96, 29.56 ppm. IR (ATR diamond): $\tilde{\nu}$ = 1676, 1604, 1567, 1556, 1506, 1479, 1446, 1422, 1398, 1337, 1320, 1225, 1191, 1139, 1112, 1078, 1046, 1023, 1011 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{12}N_3O_2$ $[M + H]^+$ 278.0924; found 278.0932.

Supporting Information (see footnote on the first page of this article): Full structural assignment of ^{1}H and ^{13}C NMR spectroscopic data of representative compounds **33a**,**g**,**i**,**k**.

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